

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10419 A1

(51) International Patent Classification⁷: A61K 9/46

(21) International Application Number: PCT/IB00/01083

(22) International Filing Date: 1 August 2000 (01.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/IB99/01386 4 August 1999 (04.08.1999) IB

(71) Applicant (for all designated States except US): RAN-
BAXY LABORATORIES LIMITED [IN/IN]; 19, Nehru
Place, New Delhi 110 019 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): TALWAR, Naresh
[IN/IN]; L-48-B, Malviya Nagar, New Delhi 110 017
(IN). STANFORTH, John, N. [GB/GB]; High Trees,
170 Bloomfield Road, Bath, Somerset BA2 2AU (GB).
TOBYN, Michael, J. [GB/GB]; 18 Queens Club Gardens,
Trowbridge, Wiltshire BA14 9SS (GB).

(74) Common Representative: RANBAXY LABORA-
TORIES LIMITED; c/o Jayadeep R. Deshmukh. 600
College Road East, Suite 2100, Princeton, NJ 08540 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: HYDRODYNAMICALLY BALANCING ORAL DRUG DELIVERY SYSTEM

(57) Abstract: The present invention relates to a gastro-retentive oral drug delivery system comprising a highly porous matrix comprising at least one drug substance, sugar(s), gas generating components and optionally, pharmaceutically acceptable auxiliary components. The pharmaceutical composition, either in the form of pellets (multiparticulate or single unit dosage form), beads, granules or capsules, is retained in the stomach while selectively delivering the drug(s) at gastric levels and upper parts of the small intestine over an extended period of time.

WO 01/10419 A1

activity and to achieve better therapeutic efficacy for the diseases which are confined to the upper parts of the gastrointestinal tract such as peptic and duodenal ulcers.

5 It is readily apparent that a sustained release formulation which slowly releases medicament over an extended period and is retained in the upper parts of gastrointestinal tract for a prolonged period would be desirable for such diseases.

10 The prior art discloses various approaches for therapeutic dosage forms which are designed to be retained in the upper parts of the gastrointestinal tract and possess sustained release characteristics.

15 U.S. Patent No. 5,780,057 discloses a pharmaceutical tablet having a multilayer structure wherein at least one layer swells in the presence of biological aqueous fluids resulting in an increase by at least 50% of the total volume of the tablet and thereby allegedly exhibiting a high residence time in the stomach and/or in the upper portion of the gastrointestinal tract. The swellable layer, being a granular mixture of biocompatible hydrophilic polymers and highly swellable (super disintegrating) polymers, allegedly acts as a barrier and allegedly modulates the slow release of the active ingredient from the pharmaceutical form. It is believed that the expanded dosage forms 20 could block the pyloric sphincter or could cause unfavorable conditions following multiple dosing resulting from retention of swollen dosage units in the stomach.

HYDRODYNAMICALLY BALANCING ORAL DRUG DELIVERY SYSTEM

FIELD OF THE INVENTION

5 The present invention relates to a gastro-retentive oral drug delivery system comprising a highly porous matrix comprising at least one drug substance, sugar(s), gas generating components and optionally, pharmaceutically acceptable auxiliary components. The pharmaceutical composition, either in the form of pellets (multiparticulate or single unit dosage form),
10 beads, granules or capsules, is retained in the stomach while selectively delivering the drug(s) at gastric levels and upper parts of the small intestine over an extended period of time.

BACKGROUND OF THE INVENTION

 An orally administered drug delivery system is exposed to a wide range
15 of highly variable conditions, such as pH, agitation intensity, gastric emptying times and composition of the gastrointestinal fluids during its transit through the digestive tract. In addition, presence of food in the tract may affect the dosage form performance. Therefore, to design an optimum oral controlled release system it is necessary to take into account the physico-chemical and
20 physiological environment of the gastrointestinal tract. The conventional approaches to controlled release formulation known in the art are not applicable to a variety of drugs having an "absorption window" in the stomach or upper parts of small intestine. Furthermore, it is advantageous to retain the dosage form in the stomach thereby increasing the contact time for local

U.S. Patent No. 5,651,985 discloses a composition comprising 30-90%, by weight of the composition, a homogenous mixture of polymers containing lactam groups and polymers containing carboxyl groups as gel forming agents, which swells to form a gel of allegedly high mechanical and dimensional stability in the aqueous environment of the stomach. It is
5 believed that as the concentration of the polymers is very high, the dosage forms containing a high dose medicament would be large and inconvenient for oral administration.

U.S. Patent No. 5,007,790 discloses a sustained-release oral drug
10 dosage form comprising a plurality of solid particles of a solid - state drug dispersed within a hydrophilic, water swellable polymer that swells on imbibition of gastric fluid to increase the particle size to a level that promotes retention in the stomach over said time period, permitting dissolution of the dispersed drug and release of the resulting solution through a leaching action.

15 The swellable polymer also allegedly maintains its physical integrity for at least a substantial portion of the time period during which the drug is released into the stomach and thereafter, rapidly dissolves. It is well recognized by those skilled in the art that it may be difficult to obtain the desired rate of release for a drug that has a high water solubility from such multiparticulate
20 systems as described in this patent, in which the drug first undergoes dissolution followed by release of the resulting solution by leaching action.

U.S. Patent No. 5,169,638 discloses a buoyancy controlled release powder formulation for releasing a pharmaceutical of a basic character

regardless of the pH of the environment and which formulation includes upto about 45% by weight of a pH dependent polymer which is a water soluble salt of a polyuronic acid and upto about 35% by weight of a pH independent hydrocolloid gelling agent having a viscosity from about 50 to about 100,000 centipoises in a 2% solution at 20°C. The said formulation allegedly floats in the gastric fluid and release the drug at a controlled rate irrespective of the pH of the environment. However, the invention is particularly adapted for release of medicaments of only basic nature. Acidic drugs are not amenable for this system.

10 U.S. Patent No. 4,814,179 discloses a floating, sustained release therapeutic composition in form of a non-compressed tablet having a network of multitudinous air holes and passages therein and a density of less than one comprising a matrix containing 0.5 - 4% gelling agent, 10-20% oil, 50-75% therapeutic agent and water. As exemplified therein, the preparation of non-
15 compressed tablet requires unconventional processing techniques and uses molds with cylindrical holes for the same. This involves manufacturing difficulties and are cost enhancing too.

U.S. Patent No. 4,702,918 discloses a floating, sustained release formulation formed by heating a mixture of a gelling agent (cellulose or starch derivative) and a fat/oil which is solid at room temperature. A sustained -
20 release capsule dosage form as disclosed therein contains a mixture of (a) from about 10 to about 90% by weight of a cellulose derivative or a starch derivative which forms a gel in water and (b) from about 90 to 10% by weight

of a higher fatty acid glyceride or higher alcohol or a mixture thereof which is solid at room temperature and (c) from 0.01 to about 85% by weight of a pharmaceutical. The capsules are prepared by filling with the said mixture of (a), (b) and (c), heating to a temperature above the melting point of fatty acid glyceride or higher alcohol and cooling and solidifying the said mixture. More than mere mixing is required to impart buoyancy to the formulation, i.e., melting followed by cooling are additional unit operations. The specific gravity of digestive fluids especially that of gastric juices is between 1.004 to 1.101. It is well known to those skilled in the art that it may be difficult to maintain the low specific gravity for the sustained release composition as described in this patent, for a prolonged period. Further, as also exemplified therein, the concentration of gelling agents and fat/oil required is high and hence the system is suited for low dose drugs, while dosage form containing high dose medicaments would be large and difficult for oral administration.

U.S. Patent No.4,126,672 discloses formulations comprising one or more medicaments in combination with a hydrocolloid or mixtures of hydrocolloids so as to have a bulk density less than one and be hydrodynamically balanced when in contact with gastric fluid. A sustained release capsule dosage form as described therein comprises finely particulate, homogenous mixture of chloriazepoxide and diazepam, about 5% to 60% by weight of therapeutically inert, pharmaceutically acceptable adjunct materials, about 0% to 60% by weight of a fatty material having a specific gravity of less than one and about 20% to 75% by weight of one or a mixture

of hydrocolloids selected from the group consisting of methyl cellulose, hydroxypropyl cellulose hydroxypropyl methylcellulose, hydroxymethyl cellulose and sodium carboxymethyl cellulose. Upon contact with gastric fluid, the hydrophilic colloid hydrates and this hydrated layer allegedly thereafter slowly dissolves to release the medicament. The release of medicament is also said to take place by leaching action at or near the surface. The hydrated colloid allegedly forms an outside barrier which retains the shape of the capsule and therefore acts to prevent the mass from disintegrating. However, it is well recognized that the application of such a system to obtain the desired rate of release of the drug wherein it is regulated by the erosion of the polymer, is difficult to maintain.

For the above stated reasons and because the prior art discloses either complicated devices and systems which are difficult to manufacture on the industrial scale or the components used therein are not so user friendly, none of the oral controlled drug delivery systems heretofore described is completely satisfactory.

Our co-pending U.S. patent application No. 09/152,932 describes a pharmaceutical composition in the form of tablets or capsules which provides a combination of spatial and temporal control of drug delivery when ingested by a patient. The pharmaceutical composition constitutes an oral controlled drug delivery system, comprising a drug, a gas generating component, a swelling agent, a viscolyzing agent and optionally a gel forming polymer. The viscolyzing agent and the gel forming polymer form a hydrated gel matrix

which entraps the gas, causing the tablet or capsule to retain in the stomach or upper part of the small intestine (spatial control) and also creates a tortuous diffusion path for the drug, resulting in sustained release of the drug (temporal control).

5 The principle of sustained release which characterizes the formulations of the subject invention is unique in the art and no teaching has been found which recognizes the application of such a porous matrix to buoyancy and sustained release as is taught by the present invention.

SUMMARY OF THE INVENTION

10 It is an object of the present invention to provide a pharmaceutical composition in the form of pellets, beads, granules or capsules which constitutes a gastro-retentive oral drug delivery system that :

- (a) generates a gas to form a highly porous (preferably honeycombed) matrix with good floating characteristics and also evolves gas upon
15 contact with gastric fluid which helps in retaining the buoyancy of the dosage form in the stomach,
- (b) provides increased gastric residence and thereby extends residency of the drug delivery system in the gastrointestinal tract,
- (c) delivers the drug at a controlled rate and exhibits reproducibility of
20 release rate into aqueous media while floating in the stomach and

- (d) provides, as compared to other oral controlled drug delivery systems, increased absorption of a drug that is absorbed largely from the upper parts of the gastrointestinal tract.

It is also an object of the present invention to provide a pharmaceutical composition constituting an oral controlled drug delivery system that maintains its physical integrity and dimensional stability when in contact with gastric fluids. The system remains floating in-vitro in the simulated gastric fluid till substantially all the drug is released.

The present invention describes a therapeutic system either in the form of beads, pellets, or granules filled in a capsule (multiparticulate system) or single unit pellets and matrix capsules (monolithic system) which constitutes an orally administered buoyant delivery system capable of extended retention in gastric fluids. The delivery system is structurally composed of a highly porous matrix (preferably honeycombed) with large volume of entrapped air which makes it light and imparts good floatation characteristics.

The therapeutic system comprises drug, sugar, gas generating components and optionally, pharmaceutically acceptable auxiliary components.

The gas generating components used herein are a combination of atleast one thermostable and atleast one thermolabile agent. During the preparation of formulation, on exposure to high temperature, the thermolabile agent generates gas and aids in attaining the porous internal structure, while the thermostable agent reacts with acidic gastric contents of the stomach to

evolve gas which helps in maintaining buoyancy of the dosage form. Thus, the combination of gas generating components permits the therapeutic system to act as a floating matrix that extends the retention of the dosage form in the stomach and also prolongs its release in the stomach and upper parts of the small intestine. That is, the system is not transported past the "absorption window" prior to releasing all or substantially all of the drug and maximum bioavailability is attained.

Preferably, the oral controlled drug delivery system of the present application which is in the form of multiparticulate or a monolithic system, comprises an amount ranging from a pharmaceutically acceptable amount up to 35% of drug, about 5% to about 90% by weight of a sugar, about 1% to about 30% by weight of the gas generating components and, pharmaceutically acceptable auxiliary components.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, the oral pharmaceutical composition includes at least one drug substance, sugar(s), a combination of gas generating agents and optionally other pharmaceutical auxiliary components which may be used by one skilled in the art to formulate the therapeutic system. The choice of auxiliary components and the amounts to be used are considered to be within the purview of one skilled in the art. It is to be borne in mind, however, that these conventional pharmaceutical auxiliary components which might adversely affect the hydrodynamic balance of the formulation of the present invention are not suitable for use therein.

The gas evolved during the preparation of the formulation by the gas generating components causes the system to attain a highly porous structure. The drug is incorporated within this highly porous, preferably honeycombed matrix.

5 The composition may be in the form of pellets, beads or granules filled within a capsule or a sachet (a multiparticulate drug delivery system) or matrix capsules and single unit pellets (monolithic system). The art of producing spherical pellets by extrusion and spheronisation techniques or spheronisation using techniques based on high shear granulation or fluidized bed techniques is well known and may be used for the preparation of pellets, beads or
10 granules in the subject invention. Single unit pellets can be produced on industrial scale using lozenge and troches cutting machines.

 Drugs which are thermostable may be added into the matrix while thermolabile drugs can be loaded onto the carrier spheres (drug free pellets)
15 using techniques of drug loading based on fluidized bed principle (equipments like Glatt) which are well known in the art. The pharmaceutical composition of the present invention may be in the form of a multiparticulate drug delivery system (up to 4mm in size pellets, granules or beads) or a single unit form as matrix capsule or large size pellets (more than 5mm in size). The matrix cap-
20 sule of the present invention may be produced by filling the powder according to the invention in a capsule made up of either gelatin, starch or hydroxypropyl methylcellulose followed with heat treatment.

Additional polymers recognized in the art of pharmaceutical compound-
ing for their release retarding properties may also be incorporated into the
gastro-retentive formulation of the present invention. These release retarding
polymers may be hydrophilic or hydrophobic in nature or may be pH depen-
5 dent or independent polymers. Examples of the polymers suitable for this
invention include hydroxypropyl methylcellulose, hydroxypropyl cellulose,
Eudragit, ethyl cellulose, xanthan gum, and the like.

The pharmaceutical composition of the present invention may be
coated with a film forming polymer to control the release of the drug or to
10 impart better/improved floating characteristics (which is a result of better
entrapment of the gas) or to improve its organoleptic properties. Furthermore,
the pharmaceutical composition may also contain bioadhesive polymers
incorporated within the coating or present as a film coat on the pellets,
granules, beads or capsules in order to improve its gastro-retentive proper-
15 ties. In another application, some highly swelling polymers may also be
added to increase the size of the dosage form so as to improve its gastric
retention.

The pharmaceutical composition of the subject invention, when added
to simulated gastric fluids, floats on the fluid till substantially all the drug is
20 released. The thermostable gas generating agent included therein reacts with
the acid present in the media and generates gases which become entrapped
within the matrix thereby enhancing the buoyancy of the formulation.

The various components of the present invention are described in more details below.

DRUG

According to the present invention, the pharmaceutical composition is
5 in the form of pellets, beads or granules filled in a capsule, a matrix capsule or
a matrix pellet, as a single unit that provides controlled release of at least one
therapeutic agent or drug. The drug may be pharmacologically active itself or
may be converted into the active form by biotransformation in the body. The
10 drug can be any drug for which therapy would be improved as a result of
controlled drug delivery and increased gastric retention.

The medicament or combination of medicaments which are amenable
to controlled release therapy utilising the novel formulations of the present
invention include any of those suitable for oral administration. The present
invention is not to be construed as being limited to any particular medicament
15 or class of medicaments.

The gastro-retentive formulations of the subject invention are partic-
ularly amenable to the administration of medicaments which are predomi-
nantly absorbed through the upper portion of the gastro intestinal tract, drugs
having pH dependent solubility, i.e., more soluble in the gastric pH as
20 compared to the intestinal pH, drugs having stomach as a site of action which
includes H-2 receptor antagonists, antacids, antimuscarinic agents, proton

pump inhibitors, drugs active against *H. pylori*, cytoprotective agents, and the like.

Illustrative examples of drugs that are absorbed predominantly from the upper parts of gastrointestinal tract include ciprofloxacin, cyclosporin, furose-
5 mide, metoprolol, oxprenolol, baclofen, allopurinol, sumatriptan, benazepril, enalapril, quinapril, moexipril, indolapril, olindapril, retinapril, spirapril, cilazeprilat, lisinopril, imidapril, benazeprilat, cilazapril, captopril, delapril, tosinopril, libenzapril, pentopril, perindopril, altiopril, quinaprilat, ramipril, spiraprilat, zofenopril, and the like; all of which are suitable for use in the present inven-
10 tion.

Drugs having the stomach as site of action include H-2 receptor antagonists such as ranitidine, famotidine, nizatidine, bifentidine, erlotidine, nifentidine, roxatidine and cimetidine, and the like; proton pump inhibitors like omeprazole, lansoprazole, pantoprazole, and the like; antacids like magne-
15 sium carbonate, aluminium hydroxide, magnesium oxide and simethicone, and the like; cytoprotectives such as sucralphate, carbenoxolone sodium and misoprostol, and the like; antimuscarinic agents like pirenzepine, telenzepine and propanthelene bromide, and the like; drugs active against *H. Pylori* like bismuth salts such as bismuth subsalicylate, tripotassium dicitratobismuthate,
20 ranitidine bismuth citrate, and the like; antibiotics for example clarithromycin, amoxycillin, and the like; all of which are suitable for use in the present invention.

Other medicaments that are suitable for this invention are drugs having solubility in acidic pH or ones having specific absorption sites in the upper part of the gastro-intestinal tract and those that are subjected to gastro-intestinal first pass metabolism (as in some reports stomach absorption is known to
5 bypass gastrointestinal first pass metabolism) include antihypertensive agents like verapamil, nifedipine, propranolol, nimodipine, nicardipine, amlodipine, prazosin, ketanserin, guanabenz acetate, hydralazine, carvedilol, methyldopa, levodopa, carbidopa; antivirals like acyclovir, inosine, pranobex, zidovudine (AZT), tribavirin, vidarabine; lipid lowering agents like simvastatin, pravastatin,
10 atorvastatin and lovastatin; antipsychotic agents like selegiline; sedatives like midazolam; all of which are suitable for use in the present invention.

The drug itself or its pharmacologically active salt or ester can be used in the present invention. Moreover, combination of drugs that are typically administered together may be included as the drug component. The amount
15 of drug is that which is typically administered for a given period of time. Accordingly, the drug may be present in amount ranging from a pharmaceutically acceptable amount up to 35% by weight of the total weight of the composition.

SUGARS

20 According to the present invention the pharmaceutical composition contains sugars which provide low density airy structure of the desired texture to the matrix. Sugars preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric

alcohol, and/or mixtures of any of the foregoing. Examples of sugars preferred for the present invention include sucrose, glucose syrup, corn syrup, crystalline fructose, fructose, lactose, dextrose, galactose, maltodextrin, maltose, and the like, sugar alcohols like sorbitol, mannitol, maltol, maltitol, xylitol, lactitol. In more preferred embodiments of the subject invention the sugar is glucose syrup either in the dried form or as a liquid. Sugars may be used alone or in combination with other similar sugars to achieve suitable matrix properties. In one preferred embodiment, sugar which is available under the brand name Glucidex (Roquette, UK) may be used.

The sugar may be present in an amount from about 5% to about 90% preferably from about 10% to about 85% and more preferably from about 15% to about 85% by weight of the total weight of the composition.

GAS GENERATING COMPONENTS

According to the present invention, the pharmaceutical composition contains a combination of thermolabile and thermostable gas generating agents which aid in the formation of highly porous, preferably honeycombed structure and enhances the buoyancy of the formulation. As the name suggests, the thermolabile gas generating agent produces gas upon exposure to high temperature (of about or less than 200°C) during heating operation while the thermostable agent does not dissociate upon exposure to temperatures stated above and produce gas upon contact with gastric fluid. Examples of thermolabile gas generating agents that may be used in the present invention include sodium bicarbonate, sodium glycine carbonate, potassium

bicarbonate, ammonium bicarbonate, sodium bisulfite, sodium metabisulfite, and the like. The thermostable gas generating agent interacts with an acid source triggered by contact with water or simply with gastric acid to generate carbon dioxide or sulphur dioxide that gets entrapped within the highly porous, preferably honeycombed matrix of the composition and improves its floating characteristics. An example of a thermostable gas generating agent is calcium carbonate and sulfites such as sodium sulfite.

In those embodiments of the present invention, where the pharmaceutical composition is in the form of a capsule, thermostable gas generating agents may be used alone or in combination with an acid source as a couple. The acid source may be one or more of edible organic acids, a salt of an edible organic acid, or mixtures thereof. Examples of organic acids that may be used as the acid source in the present invention include citric acid or its salts such as sodium citrate or calcium citrate, malic acid, tartaric acid; succinic acid, fumaric acid, maleic acid or their salts, and the like. The organic acid salts which may be used as the acid source in the present invention include, for example, a mono-alkali salt of an organic acid having more than one carboxylic acid functional group, a bialkali metal salt of an organic acid having more than two carboxylic acid functional groups, and the like.

The gas generating components may be present in amounts from about 1% to about 40 % preferably from about 1% to about 35 % and more

preferably from about 1% to about 30% by weight of the total weight of the composition.

AUXILIARY COMPONENTS

5 Optionally, other conventional pharmaceutical excipients known in the art of formulation development such as diluents; release retarding agents, inert oils, binding agents and spheronising agents may also be incorporated into the buoyant formulation of the present invention.

10 According to the present invention, the pharmaceutical composition may comprise a diluent which is stable to heating operation and form a part of the highly porous, preferably honeycombed structure. The diluent that may be used in the present invention, belongs to the class of excipients recognised in the art of pharmaceutical compounding. In preferred embodiments of the present invention, diluent is starch. Examples of starches that may be used in the present invention include maize starch, rice starch, potato starch or wheat
15 starch. Examples of other diluents include dibasic calcium phosphate, calcium sulfate, powdered cellulose, microcrystalline cellulose, and the like.

20 The diluent may be present in an amount from about 3% to about 50% by weight of the total weight of the composition, preferably from about 5% to about 40% and more preferably from about 7% to about 35% by weight of the total weight of the composition.

 The pharmaceutical composition according to the present invention may also contain polymers to retard the release of the drug. These polymers

may be present within the matrix structure of the pellets or capsules or may be coated onto the composition or may be added in capsule presentations of the present invention in the powder form. The polymers obtained as aqueous dispersions may replace water as granulating agent in the pellet preparations.

5 Solid polymers may be added directly into the powder blend.

The polymers used may be of the hydrophilic or the hydrophobic type or pH dependent or pH independent in nature. Examples of the polymers suitable for this invention include the polymers well known in the pharmaceutical art for their release retarding properties, for example, cellulose ethers
10 as hydroxypropyl celluloses of different grades, hydroxyethylcellulose, methylcellulose, hydroxypropyl ethylcellulose carboxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl methyl cellulose; acrylic polymers which are obtained as aqueous dispersions like Eudragit NE30D, Eudragit RS30D, Eudragit RL30D, Eudragit L30D or available as powders such as
15 Eudragit RSPO, Eudragit RLPO, Eudragit L10055 (all supplied by Rohm Pharma, Germany), ethyl cellulose as aqueous dispersion or in powder form. Examples of highly swellable polymers that may be used in the present invention include hydroxypropyl methylcellulose of different grades, xanthan gums, sodium alginate, and the like.

20 The release retarding polymers may also be selected from the class of natural gums as karaya gum, locust bean gum, guar gum, gellan gum, and the like.

The one or more release retarding agents from the same or two different classes may be present from about 0.3% to about 25%, preferably from about 1.0% to about 20% or more preferably from about 1.5% to about 15% by weight of the total weight of the composition.

5 According to the present invention, the pharmaceutical composition may further contain a therapeutically inert oil which is solid at room temperature but softens at higher temperatures, that is, around 50-80°C. The oil, if present, acts as a release retarding agent. The oil is preferably, a fully hydrogenated or partially hydrogenated vegetable fat or oil. Examples of oils
10 that may be used in the present invention include partially or fully hydrogenated cottonseed oil, coconut oil, soyabean oil, palm oil, kernel oil, peanut oil, sunflower oil, and the like. The oils preferred for the present invention are mentioned in the United States Pharmacopoeia as type 1 hydrogenated vegetable oils. These oils may be used alone or in combination with other oils
15 having the same characteristics.

The oil may be present in an amount from about 0.2% to about 50% preferably about 0.2% to about 45% and more preferably about 0.4% to about 35% by weight of the total weight of the composition.

20 The pharmaceutical composition in the form of beads may also include a binder to provide cohesiveness to the powder mass. The binders commonly known to the pharmaceutical art may be used in the present invention. Examples of the binders are pregelatinised starch, polyvinylpyrrolidone,

hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, starch paste, gelatin, xanthan gum, acacia, guar gum, and the like.

The binder may be present in amounts from about 0.1% to about 15%, preferably about 0.2% to about 12% and more preferably about 0.5% to about 10% by weight of the final weight of the composition.

According to the present invention, the pharmaceutical composition is prepared either in the form of pellets, granules, beads or as matrix capsules. The pellet/beads can be prepared using the commonly known techniques for extrusion and spheronisation and also other granulation techniques. Spheronising agents are added to the composition to get uniform spherical granules or pellets. Commonly used spheronisation aids are microcrystalline cellulose (Avicel PH 101 of FMC Corpn. and Emcocel 50M or Emcocel 90M of Mendell), mixture of microcrystalline cellulose and sodium carboxymethyl cellulose (Avicel RC 591 of FMC Corpn.)

The spheronising agent may be present in amounts from about 1% to about 30% preferably from about 2% to about 20% and more preferably from about 4% to about 15% by weight of the final weight of the composition.

In addition to the above ingredients, pharmaceutical grade magnesium stearate or stearic acid, and the like as a glidant, talc, and the like as an anti-adherent and silicon dioxide or hydrogenated vegetable oil or sodium stearyl fumarate, and the like as a lubricant may be incorporated in the pharmaceutical composition according to this invention.

The pharmaceutical composition in accordance to the present invention may be optionally coated with a rapidly dissolving water soluble film coat. Examples of water soluble polymers include hydroxypropyl methylcellulose, hydroxypropyl cellulose, and the like. The pharmaceutical composition may
5 be coated to a weight build up of about 1% by weight to about 10% by weight, preferably from about 1% to about 4% by weight of the total weight of the composition.

According to the present invention the capsule shell may be of a hard gelatin or a soft gelatin type. Furthermore, the capsules made of starch or
10 hydroxypropyl methylcellulose may also be used.

The present invention is illustrated by, but is by no means limited to, the following examples:

EXAMPLE 1

This example illustrates the present invention in the form of pellets in
15 which Eudragit NE 30 D has been used as a release retarding polymer in conjunction with hydrogenated vegetable oil within the matrix. The active ingredient is Diltiazem Hydrochloride. The pharmaceutical composition is given in Table 1.

TABLE 1

INGREDIENTS	% W/W
Diltiazem Hydrochloride	20.40
Hydrogenated cottonseed oil (Lubritab)	16.48
Starch (Maize)	22.09
Dried Glucose Syrup (Glucidex 40*)	16.48
Pregelatinised starch (Starch 1500)	1.32
Microcrystalline cellulose (Avicel PH 101)	9.88
Ammonium Bicarbonate	2.75
Calcium Carbonate	4.95
Eudragit NE 30D	5.65 (as solids)

*Dextrose equivalent – 40%

5 Diltiazem Hydrochloride, Hydrogenated cottonseed oil, Starch, Glucose
syrup, Pregelatinised starch, Microcrystalline cellulose, Ammonium bicarbon-
ate and Calcium carbonate were sieved through a sieve (British Standard
Sieve (BSS) 44; 355 µm) and mixed. The blend was granulated with Eudragit
NE 30 D dispersion and extruded through an extruder (GA 65, Alexander-
werk) fitted with 3.5 mm roller. The extrudates were spheronised in a
10 spheronizer (Caleva 120mm) for 20 minutes. The pellets thus obtained were
dried in an oven maintained at 120°C for 25 minutes. The pellets were
allowed to cool down to room temperature.

The pellets were tested for their floating properties and drug release in
900ml of 0.1N HCl using USP Apparatus 2 (paddle type) at 50 rpm. The
15 pellets equivalent to 30 mg of Diltiazem Hydrochloride were added to the
dissolution vessel.

At periodic time intervals the visual observations were made to check buoyancy of the pellets, if any. It was noted that all the pellets remained floating until 21 hours. The samples of the dissolution media were periodically withdrawn and analysed for Diltiazem content spectrophotometrically. The results are shown in Table 2.

TABLE 2

TIME (HRS)	CUMULATIVE % RELEASE
1	53.95
2	67.95
3	76.91
4	85.00
5	88.42

EXAMPLE 2

This example illustrates the present invention in the form of matrix capsules using Propranolol Hydrochloride as an active agent. The pharmaceutical composition is illustrated in Table 3.

TABLE 3

INGREDIENTS	% W/W
Propranolol Hydrochloride	20.00
Hydrogenated cottonseed oil (Lubritab)	22.86
Starch (Maize)	14.28
Dried Glucose Syrup (Glucidex 40*)	28.58
Ammonium Bicarbonate	7.14
Calcium Carbonate	7.14

*Dextrose equivalent - 40%

Propranolol hydrochloride, Starch, Hydrogenated vegetable oil,
5 Glucose syrup, Ammonium bicarbonate and Calcium carbonate were together
sieved through a sieve (British Standard Sieve (BSS) 44, 355 μ m) and mixed.
The blend was manually filled in size-2 gelatin capsules. The average
capsule fill weight of the composition was 320 mg. The filled capsules were
kept in an oven maintained at 110°C for 2.5 minutes, following which they
10 were cooled to room temperature.

The capsules were tested for their buoyancy and drug release in a
900ml of 0.1N HCl using USP Apparatus 2 (paddle) at 50 rpm. At periodic
time intervals the visual observations were carried out to see the buoyancy of
the capsules. It was noted that the capsules remained buoyant till 20 hours.
15 The samples of the media were periodically withdrawn and tested for
propranolol content spectrophotometrically. The dissolution results are
recorded in Table 4.

TABLE 4

TIME (HRS)	CUMULATIVE % RELEASE
1	12.41
2	21.02
4	34.06
20	81.71

EXAMPLE 3

- 5 This example illustrates single unit pellets (6 to 8 mm in diameter) which may be used as single unit dosage forms, containing Diltiazem Hydrochloride as an active ingredient. The pharmaceutical composition is illustrated in Table 5.

TABLE 5

INGREDIENTS	% W/W
Diltiazem Hydrochloride	22.37
Hydrogenated cottonseed oil (Lubritab)	10.28
Starch (Maize)	30.30
Dried Glucose Syrup (Glucidex 40*)	12.12
Pregelatinised starch (Starch 1500)	6.04
Microcrystalline cellulose (EMCOCEL 50M)	9.62
Ammonium Bicarbonate	3.87
Calcium Carbonate	5.40

10 *Dextrose equivalent -40%

Diltiazem Hydrochloride, Hydrogenated cottonseed oil, Starch, Glucose syrup, Pregelatinised starch, Microcrystalline cellulose, Ammonium bicarbon-

ate and Calcium carbonate were sieved through 355 μm mesh (British Standard Sieve (BSS) 44) and mixed. The blend was granulated with water to get a dough like consistency. The dough was rolled into cylindrical shape and small pieces weighing for 30 mg of Diltiazem Hydrochloride were cut out and manually rolled into spherical shape.

The pellets were dried in an oven maintained at 120°C for 10 minutes following which they were allowed to cool down to room temperature. The pellets were characterised for floating and drug release as described in Example 1. The pellets were found to float on the media for 20 hours. The dissolution results are recorded in Table 6.

TABLE 6

TIME (HRS)	CUMULATIVE % RELEASE
1	36.29
2	52.39
3	67.06
4	75.14
5	82.97
6	86.72
7	87.74

EXAMPLE 4

This example illustrates the capsule type of dosage form in which an organic acid is used in combination with the gas generating agents as a couple. The pharmaceutical composition is given in Table 7.

TABLE 7

INGREDIENTS	% W/W
Propranolol Hydrochloride	21.46
Hydrogenated cottonseed oil (Lubritab)	28.06
Starch (Maize)	10.52
Dried Glucose Syrup (Glucidex 40*)	22.45
Citric acid, anhydrous	3.51
Ammonium Bicarbonate	7.00
Calcium Carbonate	7.00

* Dextrose equivalent - 40%

5 All the ingredients were sieved through 355 µm mesh (British Standard Sieve (BSS), 44) and mixed. The blend was filled manually in size-2 gelatin capsules. The average fill weight was 320 mg. The capsules were given heat treatment at 110°C for 2.5 minutes, following which they were cooled to room temperature.

10 The capsules were tested for in-vitro dissolution and floating characteristics as described in Example 2. The capsules remained floating on the dissolution media throughout the dissolution test of 24 hours. Dissolution results are recorded in Table 8.

TABLE 8

TIME (HRS)	CUMULATIVE % RELEASE
1	22.77
2	33.46
4	49.06
6	60.18
10	73.24
24	86.39

EXAMPLE 5

5 The present example illustrates the capsule type of dosage form made according to the present invention containing a polymer within the matrix (xanthan gum) together with the gas generating couple consisting of an organic acid and the gas generating agents. The blend was filled in size-2 gelatin and size-0 HPMC capsules. Table 9 illustrates the pharmaceutical composition.

TABLE 9

INGREDIENTS	% W/W
Propranolol Hydrochloride	19.41
Hydrogenated cottonseed oil (Lubritab)	25.38
Starch (Maize)	9.52
Dried Glucose Syrup (Glucidex 40*)	20.30
Citric acid, anhydrous	3.17
Xanthan Gum	9.52
Ammonium Bicarbonate	6.35
Calcium Carbonate	6.35

*Dextrose equivalent - 40%

All the ingredients were weighed and passed through 355 μ m mesh (British Standard Sieve (BSS), 44) and mixed. The blend was filled manually in size-2 gelatin capsules (average fill weight 325 mg) and size-0 Hydroxypropyl methylcellulose capsules (average fill weight 520 mg). The capsules were kept in an oven maintained at 110° C for 2.5 minutes, following which they were cooled to room temperature.

The capsules were tested for floating characteristics and dissolution profile as described in Example 2. The capsules remained floating on the top of the media for 24 hours. Dissolution results are recorded in Table 10.

TABLE 10

TIME (HOURS)	CUMULATIVE % RELEASE	
	SIZE 2	SIZE 0
1	19.02	6.60
2	32.15	19.52
4	57.54	50.24
6	73.42	70.59
10	87.80	88.09
24	92.41	95.08

EXAMPLE 6

This example illustrates the present invention in the form of capsule formulation using carvedilol as an active agent. The pharmaceutical composition is illustrated in Table 11.

TABLE 11

INGREDIENTS	% W/W
Carvedilol	10.00
Dried Glucose Syrup	79.50
Calcium carbonate	6.00
Ammonium bicarbonate	2.00
Sodium Alginate	2.00
Hydrogenated cottonseed oil (lubritab)	0.50

5

All the ingredients were sieved through 180 μ mesh (British Standard Sieve (BSS), 85) and were blended in a mixer (Turbula mixer) for 30 minutes. The blend was filled manually in size-0 gelatin capsules. The average fill weight was 500 mg. The capsules were given heat treatment at 100°C for 9.0 minutes, following which they were cooled to room temperature.

10

The capsules were tested for in-vitro drug release in 1000 ml dissolution media of 0.1N HCl containing 1% sodium lauryl sulphate. The USP apparatus 2 with paddle speed at 50 rpm was used for the study. Paddles were fixed at 4.5 cm away from the base of the vessel and baskets, capped at the open end, were used as sinkers. The samples of the media were withdrawn at prescheduled timings and assayed for carvedilol content spectrophotometrically. The dissolution results are recorded in Table 12.

15

TABLE 12

TIME (HRS)	CUMULATIVE % RELEASE
0.5	15.39
1.0	27.83
2.0	47.36
3.0	58.00
4.0	63.34
6.0	71.00

EXAMPLE 7

- 5 This example illustrates the present invention in the form of capsule dosage form. The active ingredient is carvedilol. The pharmaceutical composition is given in Table 13.

TABLE 13

INGREDIENTS	% W/W
Carvedilol	9.99
Dried Glucose Syrup	79.65
Calcium carbonate	5.99
Ammonium bicarbonate	1.99
Xanthan Gum	1.59
Sodium Stearyl fumarate	0.79

10

The capsule dosage form was prepared as described in Example 6. The capsules were given heat treatment at 100°C for 13 minutes, following which they were cooled to room temperature.

The capsules were evaluated for dissolution profile as described in Example 6. The dissolution results are tabulated in Table 14.

TABLE 14

TIME (HRS)	CUMULATIVE % RELEASE
0.5	11.95
1.0	29.63
2.0	63.70
3.0	80.24
4.0	90.34

5

EXAMPLE 8

This example illustrates the present invention in the capsule dosage form using pravastatin sodium as the active ingredient. The pharmaceutical composition is given in Table 15.

10

TABLE 15

INGREDIENTS	% W/W
Pravastatin sodium	8.10
Dried Glucose Syrup	74.77
Calcium carbonate	5.72
Ammonium bicarbonate	1.91
Xanthan Gum	7.62
Hydrogenated cottonseed oil (lubritab)	1.91

The pharmaceutical composition was prepared as described in Example 6. The average fill weight of capsules was 525 mg. The capsules

were given heat treatment at 100°C for 7.5 minutes, following which they were allowed to cool to room temperature.

5 The dosage form was characterised for drug release in 1000 ml water using USP apparatus 2 (paddle type) at 50 rpm. The samples of the media were withdrawn at regular time intervals and analysed for pravastatin content spectrophotometrically. The results are shown in Table 16.

TABLE 16

TIME (HRS)	CUMULATIVE % RELEASE
0.5	9.15
1.0	19.54
2.0	36.89
3.0	55.19
4.0	74.76
5.0	93.91

10

EXAMPLE 9

This example illustrates the present invention in the form of matrix capsules using pravastatin sodium as an active ingredient. The pharmaceutical composition is illustrated in Table 17.

TABLE 17

INGREDIENTS	% W/W
Pravastatin sodium	7.73
Dried Glucose Syrup	71.37
Calcium carbonate	5.46
Ammonium bicarbonate	1.82
Xanthan Gum	7.28
Microcrystalline cellulose (Emcocel 90M)	4.55
Hydrogenated cottonseed oil (lubritab)	1.82

5 The pharmaceutical composition was prepared as described in Example 6. The average fill weight of capsules was 550 mg. The capsules were given heat treatment at 100°C for 7.0 minutes, following which they were allowed to cool to room temperature.

The dosage form was evaluated for dissolution profile as described in Example 8. The dissolution results are recorded in Table 18.

10

TABLE 18

TIME (HRS)	CUMULATIVE % RELEASE
0.5	10.79
1.0	20.68
2.0	39.01
3.0	59.44
4.0	81.75
6.0	99.22

While the invention has been described by reference to specific examples, this was for the purpose of illustration only. Numerous alternative embodiments will be apparent to those skilled in the art and are considered to be within the scope of this invention.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition which constitutes an oral drug delivery system for prolonged gastric retention having a highly porous matrix, comprising at least one drug substance, sugar(s), a gas generating component which is a combination of at least one thermostable and at least one thermolabile component, and optionally pharmaceutically acceptable auxiliary components wherein the pharmaceutical composition substantially maintains its hydrodynamic balance and physical integrity for the time period during which the drug(s) is/are released into the stomach.
2. A pharmaceutical composition according to claim 1 wherein the drug comprises at least one active compound selected from the therapeutic category of antiulcer, analgesic, antihypertensive, antibiotic, anti-psychotic, anticancer, antimuscarinic, diuretic, antimigraine, antiviral, anti-inflammatory, sedatives, antidiabetic, antidepressant, antihistaminic, antiparasitic, antiepileptic, lipid lowering drugs, and mixtures thereof.
3. A pharmaceutical composition according to claim 1 wherein the drug is selected from the group consisting of enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil, carvedilol, nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, pravastatin, lovastatin, selegiline, midazolam,

fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac, nefazodone, and mixtures thereof.

4. A pharmaceutical composition according to claim 1 wherein the drug is present in an amount ranging from a pharmaceutically acceptable amount up to 35% by weight of said composition.
5. A pharmaceutical composition according to claim 1 wherein the sugar is selected from a group comprising of saccharide and polyhydric alcohol and mixtures thereof.
6. A pharmaceutical composition according to claim 5 wherein sugar is selected from the group consisting of sucrose, glucose syrup, corn syrup, fructose, lactose, dextrose, galactose, maltose, maltodextrin, sorbitol, mannitol, maltol, maltitol, xylitol and lactitol.
7. A pharmaceutical composition according to claim 1 wherein the sugar comprises about 5% to about 90% by weight of said composition.
8. A pharmaceutical composition according to claim 1 wherein the sugar comprises about 10% to about 85% by weight of said composition.
9. A pharmaceutical composition according to claim 1 wherein the sugar comprises about 15% to about 85% by weight of said composition.

10. A pharmaceutical composition according to claim 1 wherein the gas generating component comprises a sulfite, a carbonate or a bicarbonate salt.
11. A pharmaceutical composition according to claim 10 wherein the gas generating component is selected from the group consisting of ammonium bicarbonate, calcium carbonate, sodium bicarbonate, potassium bicarbonate, sodium glycine carbonate, sodium sulfite, sodium bisulfite and sodium metabisulfite.
12. A pharmaceutical composition according to claim 1 wherein the gas generating component comprises a gas couple comprising a thermostable gas generating salt and an edible organic acid or a salt of an edible organic acid.
13. A pharmaceutical composition according to claim 12 wherein the edible organic acid is selected from the group consisting of citric acid, ascorbic acid, tartaric acid, succinic acid, fumaric acid, malic acid, maleic acid, glycine, sarcosine, alanine, taurine and glutamic acid.
14. A pharmaceutical composition according to claim 1 wherein the gas generating component comprises about 1% to about 40% by weight of said composition.

15. A pharmaceutical composition according to claim 1 wherein the gas generating component comprises about 1% to about 35 % by weight of said composition.
16. A pharmaceutical composition according to claim 1 wherein the gas generating component comprises about 1% to about 30% by weight of said composition.
17. A pharmaceutical composition according to claim 1 wherein the pharmaceutical auxiliary component is selected from the group comprising of diluents, release retarding agents, inert oils, binding agents and spheronising agents.
18. A pharmaceutical composition according to claim 17 wherein diluent is selected from the group consisting of starch, starch derivatives, cellulose derivatives, dibasic calcium phosphate and calcium sulfate.
19. A pharmaceutical composition according to claim 17 wherein the diluent is starch.
20. A pharmaceutical composition according to claim 19 wherein starch is selected from the group consisting of maize starch, rice starch, potato starch and wheat starch.

21. A pharmaceutical composition according to claim 17 wherein the diluent comprises about 3% to about 50% by weight of said composition.
22. A pharmaceutical composition according to claim 17 wherein the diluent comprises about 7% to about 35 % by weight of said composition.
23. A pharmaceutical composition according to claim 17 wherein the release retarding agent is either incorporated into the matrix or coated onto said composition.
24. A pharmaceutical composition according to claim 17 wherein the release retarding agent is selected from the group consisting of cellulose ethers, acrylic polymers, natural gums, and mixtures thereof.
25. A pharmaceutical composition according to claim 24 wherein the cellulose ethers is selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl ethylcellulose, methylcellulose, ethyl cellulose carboxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl methylcellulose, and mixtures thereof.

26. A pharmaceutical composition according to claim 24 wherein the acrylic polymer is selected from the group consisting of methacrylates, polyacrylates copolymers, and mixtures thereof.
27. A pharmaceutical composition according to claim 24 wherein the natural gum is selected from the group consisting of xanthan gum, karaya gum, locust bean gum, sodium alginate, guar gum, gellan gum, and mixtures thereof.
28. A pharmaceutical composition according to claim 17 wherein the release retarding agent comprises about 0.3% to about 25% by weight of said composition.
29. A pharmaceutical composition according to claim 17 wherein the release retarding agent comprises about 1.5% to about 15% by weight of said composition.
30. A pharmaceutical composition according to claim 17 wherein inert oil comprises a partially or fully hydrogenated vegetable oil.
31. A pharmaceutical composition according to claim 17 wherein the inert oil is selected from the group consisting of partially or fully hydrogenated cottonseed oil, castor oil, coconut oil, kernel oil, palm oil, soyabean oil, peanut oil, and mixtures thereof.

32. A pharmaceutical composition according to claim 17 wherein the inert oil comprises about 0.2% to about 50% by weight of said composition.
33. A pharmaceutical composition according to claim 17 wherein the inert oil comprises about 0.4% to about 35% by weight of said composition.
34. A pharmaceutical composition according to claim 17 wherein the binding agent is selected from the group consisting of pregelatinised starch, polyvinylpyrrolidone, gelatin, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, natural gums, and mixtures thereof.
35. A pharmaceutical composition according to claim 17 wherein the binding agent comprises about 0.1 % to about 15 % by weight of said composition.
36. A pharmaceutical composition according to claim 17 wherein the binding agent comprises about 0.5% to about 10% by weight of said composition.
37. A pharmaceutical composition according to claim 17 wherein the spheronising agent is microcrystalline cellulose or a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose.

38. A pharmaceutical composition according to claim 17 wherein the spheronising agent comprises about 1% to about 30% by weight of said composition.
39. A pharmaceutical composition according to claim 17 wherein the spheronising agent comprises about 4% to about 15% by weight of said composition.
40. A pharmaceutical composition according to claim 1 further comprising a bioadhesive polymer.
41. A pharmaceutical composition according to claim 1 further comprising a highly swellable polymer.
42. A pharmaceutical composition according to claim 1 being formed into a physical form selected from the group consisting of multiple or single unit pellets, beads, granules, soft gelatin shell capsules and hard gelatin shell capsules.
43. A pharmaceutical composition according to claim 42 wherein the form of pellets, beads or granules is coated with a pharmaceutically acceptable film forming polymer or a pharmaceutical excipient.

44. A pharmaceutical composition according to claim 42 wherein the capsule shell is made of gelatin, hydroxypropyl methylcellulose or starch.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB00/01083

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/48

US CL : 424/488

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/488

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

BRS, DERWENT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,292,518 A (KUHRIS) 08 March 1994, see entire document, example 2	1-44

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"A" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

03 DECEMBER 2000

Date of mailing of the international search report

05 JAN 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3250

Authorized officer

TODD D WARE

Telephone No. (703) 308-1235

UNIQUEMENT A TITRE D'INFORMATION

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publiant des demandes internationales en vertu du PCT.

AL	Albanie	ES	Espagne	LS	Lesotho	SI	Slovénie
AM	Arménie	FI	Finlande	LT	Lituanie	SK	Slovaquie
AT	Autriche	FR	France	LU	Luxembourg	SN	Sénégal
AU	Australie	GA	Gabon	LV	Lettonie	SZ	Swaziland
AZ	Azerbaïdjan	GB	Royaume-Uni	MC	Monaco	TD	Tchad
BA	Bosnie-Herzégovine	GE	Géorgie	MD	République de Moldova	TG	Togo
BB	Barbade	GH	Ghana	MG	Madagascar	TJ	Tadjikistan
BE	Belgique	GN	Guinée	MK	Ex-République yougoslave de Macédoine	TM	Turkménistan
BF	Burkina Faso	GR	Grèce	ML	Mali	TR	Turquie
BG	Bulgarie	HU	Hongrie	MN	Mongolie	TT	Trinité-et-Tobago
BJ	Bénin	IE	Irlande	MR	Mauritanie	UA	Ukraine
BR	Brésil	IL	Israël	MW	Malawi	UG	Ouganda
BY	Bélarus	IS	Islande	MX	Mexique	US	Etats-Unis d'Amérique
CA	Canada	IT	Italie	NE	Niger	UZ	Ouzbékistan
CF	République centrafricaine	JP	Japon	NL	Pays-Bas	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norvège	YU	Yougoslavie
CH	Suisse	KG	Kirghizistan	NZ	Nouvelle-Zélande	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	République populaire démocratique de Corée	PL	Pologne		
CM	Caméroun	KR	République de Corée	PT	Portugal		
CN	Chine	KZ	Kazakhstan	RO	Roumanie		
CU	Cuba	LC	Sainte-Lucie	RU	Fédération de Russie		
CZ	République tchèque	LI	Liechtenstein	SD	Soudan		
DE	Allemagne	LK	Sri Lanka	SE	Suède		
DK	Danemark	LR	Libéria	SG	Singapour		
EE	Estonie						